

## REVIEW

# Hiccup in adults: an overview

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**ABSTRACT:** Hiccup is a forceful, involuntary inspiration commonly experienced by fetuses, children and adults. Its purpose is unknown and its pathophysiology still poorly understood. Short hiccup bouts are mostly associated with gastric distention or alcohol intake, resolve spontaneously or with simple folk remedies and do not require medical attention. In contrast, prolonged hiccup is a rare but disabling condition which can induce depression, weight loss and sleep deprivation. A wide variety of pathological conditions can cause chronic hiccup: myocardial infarction, brain tumour, renal failure, prostate cancer, abdominal surgery etc. Detailed medical history and physical examinations will often guide diagnostic investigations (abdominal ultrasound, chest or brain CT scan...). Gastric and duodenal ulcers, gastritis, oesophageal reflux and oesophagitis are commonly observed in chronic hiccup patients and upper gastrointestinal investigations (endoscopy, pH monitoring and manometry) should be included in the diagnostic evaluation systematically. Etiological treatment is not always available and chronic hiccup treatment has classically relied on metoclopramide and chlorpromazine. Recently, baclofen (LIORESAL) has emerged as a safe and often effective treatment.

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Hiccup, or singultus, is a spasmodic, involuntary contraction of the inspiratory muscles, associated with delayed, abrupt glottic closure, causing a peculiar sound. Most of our knowledge of this phenomenon relies on experiments carried out by NEWSOM DAVIS [1] in 1970, though descriptions and pathophysiological concepts appear in early medical literature [2]. In the foetus, hiccup is normally present after the eighth week of gestation during behavioural active phases and tends to persist after birth in premature infants [3-6]. Short hiccup spells are commonly experienced by healthy children and adults, but transient episodes do not require medical attention. They disappear spontaneously or with simple measures, such as breath-holding, or swallowing a spoonful of sugar.

In contrast, prolonged hiccup attacks, lasting more than 48 h, or recurring in spite of various treatments, are rare but distressing. Such hiccups must not be underestimated by the physician; they may cause insomnia, wasting, exhaustion and depression [7-16]. If an underlying cause is diagnosed [16, 17], aetiological treatment may relieve the patient from persistent hiccup. However, when no cause has been identified, or when the underlying disease cannot be treated, symptomatic treatment is necessary.

The management of chronic hiccup is a challenge for the clinician and raises two issues: 1) how should the diagnostic evaluation be conducted? and 2) what hierarchy of treatments should be established? Recent experience with patients complaining of prolonged hiccup [16] prompted us to review the literature on chronic

hiccup in search of answers to these questions. This literature consists mainly of scores of case reports on aetiology or treatment. Lack of systematic diagnostic work-up and controlled protocols for treatments make conclusions difficult to draw from the few series that have been published. Past review articles have not provided practical guidelines for diagnostic evaluation or treatment protocols [18, 19], or have focused on patient management in the emergency department [20]. We will attempt to provide some guidelines, using data from the literature, in addition to our own experience, after a summary of hiccup pathophysiology.

## Description and pathophysiology of hiccup

The most striking feature of hiccup is the particular sound which gives its name to the phenomenon in most languages (table 1). It is generally admitted that this noise is caused by sudden glottic closure during the forceful involuntary inspiration characteristic of hiccup, and it is absent when the mouth is closed. Glottic closure takes place about 35 ms after the beginning of diaphragmatic contraction, and the glottis may remain closed for up to 1 s [1]. In infants, pharyngeal collapse may be associated [5], and this could be the case in adults also, since we have observed it endoscopically in one case. Whether glottic closure is a passive phenomenon caused by a strong negative pressure, or the consequence of adductor

laryngeal muscle contraction, is not known. Hiccup can occur at any moment of the respiratory cycle, including expiration, but typically follows peak inspiration [1, 12]. The spontaneous frequency of hiccup varies considerably between individuals, ranging from 2–60 hiccups·min<sup>-1</sup> [1, 5, 7, 12]. Although it has been reported that in the same individual, hiccup frequency and amplitude are relatively stable [1, 12], we have not observed this stability in our series [16].

Table 1. — Hiccup around the world

Hiccup, hiccough	English
Hoquet	French
Hipo	Spanish
Hikke	Norwegian, Danish
Hicka	Swedish
Hik	Dutch
Hiçkirik	Turkish
Hirik	Kurd
Geehouk	Hebrew
Hakka	Arabic (Syria)
Chouhigua	Arabic (Algeria)
Chahgua	Arabic (Morocco)
Sughitz	Roumanian
Nac	Vietnamese
Lozingas	Greek (modern)
Λψγμοσ	Greek
Ikota	Russian
Tale	Chinese
Czkawka	Polish
Schluckauf	German
Singultus	Latin, English, German
Singhiozzo	Italian
Sekseke	Parsi

In infants, who have a compliant rib cage, and to a lesser extent in adults, hiccup is accompanied by paradoxical movements of the rib cage and abdomen, typical of a strong diaphragmatic contraction against a closed airway [21].

Because of early glottic closure, the strong inspiratory effort does not result in a large change in lung volume and, therefore, ventilatory effects of hiccup are minimal in normal subjects [1]. In intubated or tracheostomized patients, some mild degree of hyperventilation and respiratory alkalosis can appear [1, 5]. In a tracheostomized patient with brainstem infarction, adequate "spontaneous" ventilation was maintained for hours by persistent hiccup alone [22].

Hiccups are commonly seen on the electrocardiogram (ECG) tracing [5, 23, 24]; the electrical signal can be used to measure hiccup frequency and its variations with various stimuli. When the clinical context is missing, they can be mistaken for premature ventricular contractions [25], although, more often, they appear as wide, upward or downward deflexions of variable amplitude. It is not clear whether they are movement artefacts or diaphragmatic action potentials [23, 26]. In a group of 10 patients, in whom analysis of hiccup and ECG was performed, a strong correlation was demonstrated between the timing of hiccup and cardiac cycle, independent of respiration, during wakefulness and sleep, (W.A. Whitelaw *et al.*, personal communication). The significance of this observation is not clear.

Fluoroscopy has been extensively used to observe diaphragmatic behaviour during hiccup, and reveals that diaphragmatic contractions may be bilateral - and that one side may be dominant - but is more commonly unilateral. The left hemidiaphragm is more frequently involved than the right. Detailed observations provided by SAMUELS [7] showed that various patterns of diaphragmatic activity exist: contraction of the whole diaphragm, but also of one or more segments, is possible. This contraction may be single or may be followed by a few smaller spasms in quick succession, a finding which has been confirmed by other studies [1, 11, 16]. However, detailed diaphragmatic electromyographic (EMG) studies to evaluate whether segments of the muscle contract differently are not available.

EMG recordings of intercostal and accessory muscle activity show that inspiratory activation is not confined to the diaphragm, but that external intercostals [1], and scalenes [11], display synchronous activity. In contrast, parasternal intercostal muscle discharge is delayed, and the sternomastoid muscle, an accessory inspiratory muscle, has a variable activity [1]. Simultaneously with inspiratory muscle activation, expiratory muscles are inhibited. The intensity of this inhibition diminishes with decreasing lung volume [1]. Phrenic nerve [11, 27] and corticodiaphragmatic [27] conductions are normal.

Onset of hiccup is associated with cessation of peristalsis in the oesophagus, reduction in sphincter pressure and increased acid exposure. Oesophageal function returns to normal between hiccups, unless an oesophageal abnormality is responsible for hiccup [13, 28–31].

Very little is known about hiccup pathophysiology at the present time. A pathophysiological mechanism postulated in the 1940s remained unchallenged until the experimental study of NEWSOM DAVIS [1] in 1970. The importance of phrenic or vagal stimulation was recognized early on [32–36]. Although there was no experimental work to support this notion, hiccup was labelled a "respiratory reflex" [33, 37]. This hypothetical reflex arc includes afferent information from the phrenic nerves, the vagi and T6–T12 sympathetic fibres [10, 36], a hiccup centre located either in the brainstem [33], possibly within the respiratory centres, or in the cervical cord between C3 and C5 [10, 33], with the principal efferent limb being the phrenic nerves [36, 38]. The involvement of the nerves cited above is attested by the numerous causes of hiccup where irritation (*e.g.* manipulation of abdominal viscera during surgery), or counter irritation (*e.g.* carotid sinus massage), of their branches trigger or suppress hiccup.

In the only study which attempted to elucidate hiccup pathophysiology, NEWSOM DAVIS [1] monitored the effects of respiratory stimuli on hiccup characteristics in three subjects. Hiccup amplitude was assessed by inspiratory muscle EMG activity and flow measurement. Hypercapnia decreased hiccup frequency but had no effect on amplitude. In contrast, hypocapnia did not modify frequency but increased amplitude. Mean amplitude of hiccups was maximal during peak inspiratory flow. Because of synchronous bilateral discharge of

inspiratory muscles (diaphragm and external intercostals), the author suggested that supraspinal structures were involved in hiccup pathophysiology. No evidence in the study suggested that these structures were the inspiratory centre of the medulla as some had suggested previously [7]. In contrast to the effect on respiratory neurons, increased arterial carbon dioxide tension ( $P_{aCO_2}$ ) did not stimulate hiccup, but often put a stop to it. NEWSOM DAVIS [1] concluded that hiccup was generated by supraspinal mechanisms, independent of inspiratory centres, with interaction with behavioural and chemical respiratory influences at the spinal level.

Suppression of inhibitory influences on a supraspinal hiccup centre could lower the threshold and allows hiccup to start. This mechanism was suggested to explain the occurrence of persistent hiccup in multiple sclerosis or in metabolic disorders [39]. It has also been used to account for a higher incidence of hiccup in the foetus and premature infant than in adults; with development and central nervous system maturation, the hiccup centre would receive its normal inhibitory input, occasionally interrupted by irritation due to peripheral stimuli [3].

It has also been suggested, based on electroencephalogram (EEG) findings in patients with epilepsy, that chronic hiccup was the result of seizure activity [40, 41].

This would explain the occurrence of chronic hiccup in patients with cerebral disorders, and the efficacy of anti-epileptic drugs. However, most patients suffering from chronic hiccup do not have any cerebral dysfunction and diazepam, a major anti-convulsant drug, can trigger or worsen hiccup [41].

### Acute hiccup

In healthy adults and children, acute hiccup may be caused by gastric distension (following overeating, eating too quickly, drinking carbonated beverages), ingestion of spicy, very hot or very cold food, excessive alcohol intake, or endoscopic examination of the upper gastrointestinal tract [34, 36, 42–46]. It can be triggered by emotional factors, such as shock, fear, laughter or over-excitement [7, 17, 34, 35, 42], or by rapid changes in temperature [44]. It is not known whether acute hiccup can occur in the absence of one of these triggering factors. Most hiccups will stop spontaneously, but when they last more than a few minutes, or become an embarrassment, the attack is generally easily ended by one of the simple manoeuvres listed in table 2 and hiccup has no consequence in healthy subjects.

Table 2. — Non-pharmacological treatment of hiccup

#### 1) Common remedies

##### Respiratory manoeuvres

Breathholding [1, 34, 35, 42], associated with: neck extension [47], quickly drinking a large glass of water \*, steady inspiratory effort against closed airway [1], application of 20–40 cmH<sub>2</sub>O CPAP [38, 48]  
Coughing [1], Valsalva manoeuvres [5],  
hyperventilation [34, 43]  
Rebreathing in a bag [34, 42, 43], or breathing a 5% CO<sub>2</sub> mixture [1, 7, 36, 42, 43]  
Compression of the diaphragm by drawing legs up [34] or leaning forward [36], compression of thyroid cartilage [49]  
Application of ice or mustard plaster on epigastrium [36, 50]

##### Nasal and pharyngeal stimulation

Pressure on bridge of nose\*, sneezing [5, 35, 36, 42]  
pressure on the upper lip [43, 51]  
Inhalation or instillation of irritants (smelling salts, ether, ammonia..) [34, 52–55]  
Gargling with water [56]  
Firm traction of the tongue [34, 40]  
Drinking: from the far side of a glass [42, 57] from a glass covered with a piece of fabric\*, quickly 1 can of lemonade then lie down [58], carbonated beverages\*, ice water [36], alcohol, tea, [1], vinegar [10], sweet pickle juice [59]  
Swallowing granulated sugar [60–62], crushed ice or stale bread [10], crushed pepper\*,  
Ingestion of a sugar lump dipped in vinegar\*, lemon wedge and Angostura bitter [45]

Touch soft palate with tip of the tongue then swallow\*, posterior pharyngeal wall stimulation [10],  
massage of hard/soft palate junction [63]

##### Miscellaneous vagal stimulation

Ocular compression [43], carotid massage [34, 42],  
digital rectal massage [64, 65]

##### Psychiatric treatments

Behavioural therapy [11, 66–68], hypnosis [69–72]

##### Gastric distension relief

Fasting for 24 h [1, 58], gastric aspiration [42], or lavage [20, 36, 43, 46], vomiting [11, 34, 36, 43, 46]

##### Other remedies

Bilateral compression of radical arteries, while gazing into the subject's eyes [73], rest in bed [74]  
fright [34, 42, 43, 75], acupuncture [76, 77]  
prayers [78], wrap patients in wet, cold sheets [50], hydrotherapy [79], relaxation\*, concentration\*, bilateral pressure on external auditory meatus [80], homeopathy\*, mesotherapy\*, pinching the external side of the wrist\*

#### 2) Phrenic nerve disruption

##### Transient disruption:

Cooling [42, 81, 82]  
Local anaesthetic injection [81, 83, 84]  
Compression of phrenic nerve at the neck [85, 86]  
Phrenic nerve stimulation [7, 84, 87]

##### Phrenic crush or section:

Bilateral [43, 51, 88–90]  
Unilateral [43, 49, 91–93]

CPAP: continuous positive airway pressure.\*: remedies communicated to us by patients or physicians aware of our interest in hiccup.

BROUILLETTE *et al.* [5] demonstrated that hiccup is potentially harmful in premature infants under observation in the intensive care unit. In unintubated babies, decreased respiratory frequency at the onset of hiccup spells, and a larger number of obstructed breaths, resulted in oxygen desaturation and relative bradycardia. After a few minutes, respiratory parameters and heart rate returned to pre-hiccup baseline value. Hiccup did not influence breathing frequency in intubated babies, but resulted in mild hyperventilation.

Numerous cases of hiccup spells after myocardial infarction have been reported [8, 17, 69, 75, 83, 91, 94–97], and treatment should be applied as soon as possible if spontaneous resolution does not take place.

Short hiccup bouts are not unusual in the operating room. Intubation [10], positioning of the patient on the operating table [98], and manipulation of the viscera during surgery [38, 43, 99] will often cause hiccup. Independent of the surgical procedure, general or regional anaesthesia itself can also induce hiccup [36, 99–101]. The use of short-term barbiturates has been incriminated as a possible cause of hiccup during induction of anaesthesia [102]. However, in most cases, hiccup can be attributed to vagal afferent stimulation. Such hiccup spells will generally stop spontaneously [100], or with deepening of anaesthesia [99]. When hiccups persist, they can interfere with assisted ventilation or disrupt the surgical procedure and, therefore, require therapeutic measures. Ventilation with oxygen [99], and hyperventilation either alone or associated with deepening of anaesthesia [36, 99], have been used with mixed success. Application of 20–40 cmH<sub>2</sub>O of continuous positive airway pressure (CPAP) for a few minutes [38, 43, 48], nasal instillation of 1 ml of ether [52], CO<sub>2</sub> rebreathing [43], or pharyngeal stimulation with a nasal catheter [10], can be effective. If these methods fail to suppress hiccups, a pharmacological treatment can be applied. The following drugs have been effective in anaesthetized patients: atropine [43, 99], chlorpromazine and metoclopramide [103], pentobarbital [99, 103]; methylphenidate [11, 100, 104], edrophonium [99], pentazocine [105].

### Chronic hiccup

Chronic hiccup has been defined as a hiccup spell lasting more than 48 h, or recurring hiccup attacks [17, 18]. According to the Guinness Book of Records, the world champion is an American subject who has been hiccupping for the last 68 yrs [78]. Duration of hiccup bouts varies greatly from patient to patient, and depends on the underlying cause, as well as the efficacy of treatments.

In our experience, however, the physician is confronted with three distinct situations in which the consequences of hiccup as well as treatment outcome are drastically different. Firstly, patients may complain of hiccups which have been present for several days or weeks and when the appropriate diagnostic evaluation is conducted, an underlying factor is often discovered and aetiological treatment is successful. In some instances, no aetiology is found. In our experience, spontaneous resolution of

hiccup is rarely observed if the attack has lasted more than a week. Shorter hiccup spells may end spontaneously, or after treatment with chlorpromazine, metoclopramide or acupuncture. It is likely that most successful hiccup treatments reported in the literature were carried out in such patients, in whom hiccup is relatively easy to stop. The situation is different when patients, mostly elderly subjects, consult for prolonged, intractable hiccup, which has lasted for several years. Hiccup bouts and hiccup-free periods often alternate, at variable intervals. Interestingly, a fixed periodicity has been reported in patients suffering from brain tumour or injury [12–14, 41, 106, 107]. In some cases, the cause of this distressing symptom remains unclear, or is impossible to treat. In such cases, several drug trials may need to be carried out until a successful cure is identified. We have never observed spontaneous resolution of hiccup in those patients. Lastly, it is not unusual for terminally ill patients, in particular acquired immune deficiency syndrome (AIDS) and cancer patients, to be affected by recurring periods of hiccup, lasting several hours or days.

Chronic hiccup seems to be more frequently encountered in males than in females [16, 35, 108], although no explanation can be provided to account for this difference. A unique example of familial chronic hiccup was reported by LANCE and BASSIL [58]. Their patient had experienced intractable hiccup for 30 yrs. Seven members of his family suffered from the same affliction.

Consequences of chronic hiccup depend upon the length of the attack, but also upon the underlying physiological status. In prolonged hiccup attacks, eating or sleeping may be impaired (7–16, 59, 109), leading to weight loss, exhaustion, or anxiety and depression [9, 10, 16, 29, 84, 110]. In debilitated patients, particularly during acute myocardial infarction, persistent hiccup can slow down the recovery process, and even threaten the patient's life and warrant drastic therapeutic measures [51, 69, 81, 91–94]. After thoracic or abdominal surgery, hiccup may cause wound dehiscence [1, 103, 111]. Lastly, a rapid succession of hiccups may induce atrioventricular block with Adams Stokes attacks [26, 112].

Hiccup may be present during sleep, but there is no general rule. In one patient, polysomnographic data showed that hiccup persisted not only in non-rapid eye movement (NREM) sleep but also during rapid eye movement (REM) sleep, in contrast with other clonic muscle contractions. The effect of hiccup on sleep architecture in this patient was the disruption of REM sleep, but no comparison with hiccup-free period was available. Hiccup frequency decreased with deepening of sleep state and lost its rhythmicity during REM sleep [12]. Several authors report sleep deprivation due to chronic hiccup [8–15, 84]. In some instances, however, hiccup disappears during sleep [84]. In our experience, hiccup persists during sleep in more than half of the patients. We also found a remarkably high incidence of sleep disordered breathing in patients with chronic hiccup (11 out of 16 elderly male patients studied showed evidence of obstructive sleep apnoea).

### Aetiological factors of chronic hiccup

A list of medical conditions known to cause chronic hiccup is provided in table 3. Useful sorting of these numerous causes is arduous in the absence of clear pathophysiological concepts or reliable statistics on their relative frequency. We have favoured an anatomical classification, which can guide the diagnostic evaluation. Irritation of the cerebral hemispheres, brainstem, phrenic and vagal nerves or diaphragm can cause hiccup, regardless of the nature of the stimulus. The mechanism by which drugs or metabolic disorders, such as renal failure or diabetes, cause hiccup is not understood.

Because of their relative frequency, attention should be drawn to gastrointestinal causes. A number of oesophageal diseases can trigger hiccup spells, and in some instances, rapid relief of chronic hiccup by aetiological treatment demonstrates a cause-effect relationship [16, 153]. In 18 cases reported by CABANE *et al.* [16], oesophageal disorders were present in 12 cases and were considered to be responsible for hiccup in 9 subjects. In some cases, the relationship is not clearly established. Oesophageal reflux is extremely frequent in chronic hiccup. In some instances hiccup disappears with anti-reflux medications, and can be induced by an acid perfusion test [29]. However, in a recent case report, episodes of reflux were detected only during hiccup spells, thus suggesting that oesophageal reflux was a direct consequence of hiccup [13]. The two conditions can also co-exist by coincidence, and anti-reflux medical or surgical treatment may fail to relieve hiccups [16, 30, 31]. Other gastrointestinal and abdominal causes are not as frequent, and their relationship with chronic hiccup has not been investigated as thoroughly as oesophageal diseases, but they are believed to cause hiccup through irritation of vagal afferents, of the phrenic nerve, or of the diaphragm itself.

Post-operative hiccup is frequent, particularly after abdominal and prostatic surgery [17, 43, 51, 99, 105]. The attack may reveal a complication, such as abdominal or gastric distension, peritonitis, subdiaphragmatic abscess, urinary tract infection, or renal failure [44]. In addition, hiccup itself represents a complication, leading to loss of sleep, exhaustion, wound dehiscence, and pain [1, 17, 99, 111]. Effective treatment is urgent, and often relies on drugs when gastric aspiration, CO<sub>2</sub> rebreathing and pharyngeal stimulation have failed.

Psychogenic or hysterical hiccup has sometimes been diagnosed when behavioural treatment was effective, or when all investigations were negative [16, 17, 66, 127]. The diagnosis should be established with extreme caution. Psychological consequences of hiccup should not be mistaken for psychological causes. Moreover, in our experience, and that of others, repeated physical examination and investigations will often uncover an organic factor [118].

Lastly, chronic hiccup can be iatrogenic, caused by drugs such as benzodiazepines [41, 135, 136], barbiturates and corticosteroids [59, 134]. One case of chronic hiccup following traumatic insertion of a jugular vein catheter has been reported [158].

The combination of two or more aetiological factors is

not rare [26, 92, 109] and could possibly increase the risk of triggering hiccup attacks. In some patients, it may be difficult to determine the exact cause of hiccup [26, 92, 139, 147, 159]. Great variations in hiccup susceptibility between subjects are likely to exist: some of the diseases presented in table 3 are frequent, and yet chronic hiccup is uncommon. In a retrospective series of over 200 cases of persistent hiccup, a striking difference existed between males and females with respect to the presence of a cause [17]. However, bias probably explains this difference: better acceptance of psychogenic origin in female patients than in males, older age of the male patients, presence of more than one disturbance in males. Furthermore, the authors did not mention the diagnostic evaluation and whether all patients underwent the same procedures [17].

### Guidelines for the management of chronic hiccup: diagnostic evaluation and treatment

Chronic hiccup may be idiopathic, and the extensive laboratory testing suggested below may fail to reveal any cause, but it can also be the symptom of a serious underlying disease, particularly of the central nervous system. For instance, chronic hiccup has been reported as the initial and misleading symptom of multiple sclerosis [39], and brainstem tumour [106], or abscess [125]. These examples illustrate the fact that negative medical history and physical examination should not lead to the diagnosis of idiopathic or psychogenic hiccup. Although it is unrealistic to test patients for all possible causes of chronic hiccup, we believe that a diagnostic evaluation is indicated when a patient presents with a complaint of chronic hiccup. The guidelines that we offer in table 4 rely on clinical common sense and personal experience. To date, no systematic study of chronic hiccup has assessed the benefit of extensive work-up. This lack of statistics simply reflects the rarity of intractable hiccup.

The management of a patient complaining of chronic hiccup starts by obtaining a detailed medical history. Information about the chronology of hiccup bouts, the symptoms that accompany them, the persistence of hiccup during sleep, all physical and pharmacological treatments already tested, with their efficacy and side-effects, will be elicited. Any symptom suggestive of an underlying disease will be noted. In particular, the patient will be questioned about past surgical interventions, respiratory and gastrointestinal symptoms, alcohol or drug abuse. During physical examination, attention will be focused on the chest, the nervous-system, gastrointestinal and urinary tracts, as well as the neck and the pharynx. All abnormal findings will be further investigated. When a patient is seen soon after the beginning of a hiccup attack, an electrocardiogram will be obtained, to rule out atypical myocardial infarction. After the examination is completed, non-pharmacological symptomatic treatment will be applied. Patients consulting for a disabling hiccup may have attempted, without success, some of the simple methods listed in table 2. Therefore, more aggressive manoeuvres may be tested, such as CO<sub>2</sub> rebreathing or posterior pharyngeal wall stimulation with a rubber catheter introduced through the nose [10, 160].

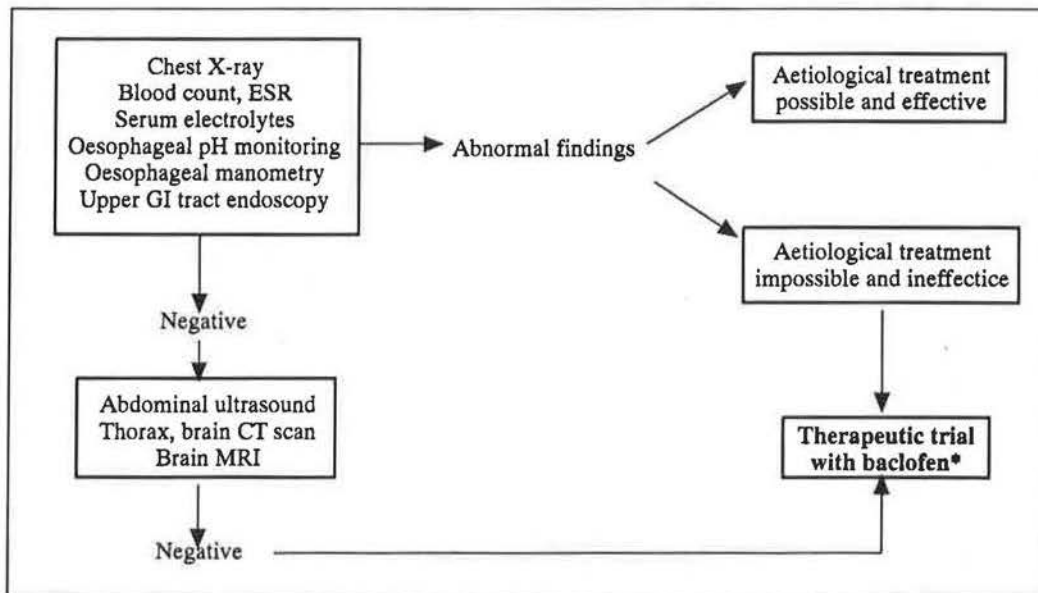
Table 3. - Aetiology of chronic hiccup

<b>Central nervous system</b>	Neck tumour or lymphadenopathy [7, 36, 44, 113]
Craniocerebral injury [7, 11, 12, 35, 36, 113]	Glaucoma [143]
Neoplastic diseases:	Hair [15, 144] or ant [145] in external auditory canal
Intracranial neoplasms [16, 34, 36, 43, 44]	
Brainstem neoplasms [106, 114, 115]	
Demyelinating diseases:	
Multiple sclerosis [8, 39, 116, 117]	
Spinal cord:	
Syringomyelia [17]	
Tabes dorsalis [7, 36, 93]	
Cervical hydromyelia [1]	
Cerebrovascular diseases:	
Ischaemic disease [7, 13, 17, 60, 118-121]	
Intracranial haemorrhage [34, 36, 90]	
Arteriovenous malformation [90]	
Temporal arteritis [17]	
Infectious diseases:	
Meningitis [34, 43]	
Encephalitis [7, 36, 42, 122, 124]	
Neurosyphilis [7, 93]	
Brain abscess [14, 16, 36, 118]	
Tuberculomas [118]	
Miscellaneous:	
Epilepsy [6, 44]	
Hydrocephalus [34]	
Ventriculo-peritoneal shunt [125]	
CNS sarcoidosis [126]	
<b>Psychiatric causes</b>	
Reaction to grief [17] or shock [7, 41]	
Hysteria [16, 17, 35, 36, 42, 71, 108, 127]	
Personality disorders [17, 33, 66, 69]	
Anorexia nervosa [17]	
Enuresis [17]	
Malingering [17, 36]	
<b>Metabolic, infectious and toxic causes</b>	
Renal failure [10, 17, 42, 128-130]	
Diabetes [7, 17, 44]	
Metabolic disorders:	
Hyponatraemia [131, 132]	
Hypocalcaemia [133]	
Hypocapnia [1]	
Hyperuricaemia [34, 43, 44]	
Combination of metabolic disorders [23, 26]	
Fever, septic shock [42, 44]	
Insulin shock therapy [43]	
Alcohol [1, 17, 29, 42]	
Drugs:	
Alpha methyl dopa [1]	
Dexamethazone [134]	
Methylprednisolone [59]	
Sulphonamides [9]	
Diazepam [41, 135]	
Midazolam [136]	
Chlordiazepoxide [137]	
Barbiturates [11, 99]	
Methsuximide [138]	
Heroin addiction [7]	
Nicotine [18]	
Etoposide [139]	
Malaria [34, 43]	
Herpes zoster [16, 140, 141]	
Typhoid fever [36, 42]	
Acute rheumatic fever [36, 142]	
Influenza [36, 44]	
<b>Ear nose and throat</b>	
Pharyngitis [15], laryngitis [43]	
Goitre [43]	
	<b>Thorax</b>
	Lung and bronchi:
	Pneumonia [23, 113, 115], bronchitis [43]
	Tuberculosis [109, 146]
	Lung cancer [36]
	Asthma [17, 44]
	Pleura:
	Pleuritis [17, 36, 42, 147]
	Empyema [36]
	Mediastinum:
	Mediastinitis [16, 36, 42]
	Tumour [7, 34, 36, 43]
	Pericarditis [7, 36, 44]
	Abscess [148]
	Cardiovascular:
	Myocardial infarction [8, 17, 69, 75, 83, 91, 94-97]
	Angina pectoris [149]
	Thoracic aortic aneurysm [7, 36, 43, 74]
	Irritation caused by foreign body [16, 150]
	Cor pulmonale [151]
	Oesophagus:
	Oesophageal cancer [17] or obstruction [16, 46, 131]
	Oesophagitis [152], oesophageal ulcers [16, 153]
	Hiatus hernia and oesophageal reflux [16, 17, 29, 34, 60]
	Diaphragm:
	Diaphragmatic hernia [7, 44]
	Diaphragmatic tumours [34, 154]
	Neurofibroma of phrenic nerve [7]
	Irritation by foreign body [16]
	Post operative [8, 17, 60, 155]
	<b>Abdomen</b>
	Gastric disorders:
	Gastric cancer [17, 34, 36], or ulcer [17]
	Gastritis [7, 34]
	Gastric distention [34, 42, 81, 151]
	Foreign body [7]
	Gastrointestinal bleeding [7, 35]
	Pancreatic disorders:
	Pancreatic cancer [156]
	Pancreatitis [7, 113, 151]
	Hepatobiliary disorders:
	Hepato- or splenomegaly [44]
	Hepatitis [42], perihepatitis [4]
	Cholecystitis [151]
	Cholelithiasis [17]
	Cirrhosis [34]
	Intestinal disorders:
	Crohn's disease, ulcerative colitis [7]
	Bowel obstruction [56]
	Peritoneum:
	Subphrenic abscess [34, 42]
	Intra-abdominal abscess [35, 36, 157]
	Appendicitis [36]
	Parasitic infection [36, 44]
	Peritonitis [44]
	Postoperative [8, 43, 51, 105]
	Cardiovascular disorders:
	Abdominal aortic aneurysm [7]
	Aortorenal graft [72]
	Irritation caused by wiring of abdominal aorta [7]
	Kidney and urinary tract:
	Hydronephrosis [17]
	Prostatic infection and cancer [17, 34, 35]
	Prostatic and urinary tract interventions [51]

Nasal instillation of ether [52], massage of the soft-hard palate junction [63], traction of the tongue [34, 40], gastric aspiration [36, 42, 43], or compression of the phrenic nerve at the neck, may be effective [86, 161]. Various vagal manoeuvres can be attempted, such as ocular compression [43], and carotid sinus massage [34, 42]. Hiccup cessation following digital rectal massage has been reported in two cases [64, 65]. However, in six patients with intractable hiccup, we found that this manoeuvre was totally unsuccessful. These remedies may suppress hiccups in a number of patients, and unless it reappears, there is no need for further laboratory investigations. However, in our experience, the success of these manoeuvres is often transitory, and seldom lasts more than a few minutes.

worsening of hiccup with these drugs. Metoclopramide and chlorpromazine are useful in postoperative cases, in order to quickly relieve hiccup. In all situations, however, we believe that diagnostic evaluation ought to be undertaken. A chest X-ray and blood test should be obtained, and in view of the cause-effect relationship between hiccup and oesophageal function, we recommend that all patients with persistent hiccup undergo gastro-oesophageal investigations (oesophageal pH monitoring and manometry, endoscopy). This will often reveal oesophagitis, gastritis or ulcers. Whether these lesions can be classified as cause or consequence of hiccup, or as a coincidence, will depend on the outcome of a therapeutic trial. When gastro-oesophageal causes have been ruled out and non-pharmacological remedies have failed,

Table 4. - Management of chronic hiccup



ESR: erythrocyte sedimentation rate; GI: gastrointestinal; CT: computed tomography; MRI: magnetic resonance imaging. \*See text below.

If they are ineffective, and providing that initial clinical assessment was negative, most authors recommend a drug trial. Because it is potent and relatively safe, preference is usually given to chlorpromazine (Largactil®, Thorazine®) (25–50 mg *i.v.*) [8, 88, 105, 110, 140, 162]. Metoclopramide (Primperan®, Maxolon®, Reglan®) (10 mg *i.v.*) has been used in a large number of patients [59, 103, 151, 163, 164]; it is unclear whether its effectiveness is related to a direct action on the CNS or to its antigastro-oesophageal reflux properties. The use of metoclopramide and chlorpromazine has been advocated in the emergency room setting [18, 20], but we believe that patients should simply be reassured (as hiccup is very seldom life-threatening), and be referred to an internist, a gastroenterologist or a pulmonologist for evaluation and treatment. If a sedative is necessary, benzodiazepines should be avoided, since some authors have shown

further diagnostic tests should be prescribed, in particular to rule out a neurological cause. The importance of diagnostic evaluation is illustrated by our findings in a population of 42 chronic hiccup patients: an aetiological factor was present in 24 cases, an upper gastrointestinal tract disorder (oesophagitis, oesophageal reflux, gastritis, bulbar ulcer, *etc.*) was present in 11 cases - although their primary or secondary nature was unclear - and in seven patients, no abnormality was found which could be related to hiccup.

If these tests do not reveal any abnormality, a wide range of pharmacological treatment can be attempted. In table 5, we have chosen to list drugs that are easily available and which have been successful in stopping chronic hiccup. Many drugs have been used, but the data concerning pharmacological treatment of hiccup mostly consist of case reports of less than five patients.

The rationale behind the choice of one drug or another, as well as explanations for the possible mechanism of action are often vague. Only one controlled trial has been carried out, in a study of 101 anaesthetized patients. In 51 cases, hiccup did not stop spontaneously, and patients were able to receive either methylphenidate or saline solution. No difference was found between the two treatments [100]. Although methylphenidate is no longer available, it still appears on some lists of treatments for chronic hiccup.

(2 mg) [108–110, 128, 170, 177]. However, amantadine, a dopamine agonist, and levodopa, associated with carbodopa, were successfully administered to one patient with chronic hiccup and Parkinson's disease [178]. In one of our patients, on the other hand, amantadine triggered a hiccup spell.

Among the wide variety of drugs used to stop chronic hiccup, nifedipine, and anticonvulsant drugs have been given some attention. Following successful treatment of hiccup with nifedipine (Adalate®, Procardia®) in one

Table 5. – Common drug treatment of hiccup†

Drug	Dosage**
Baclofen [58, 165–169]	5–60 mg <i>q.d.</i> orally
Chlorpromazine* [8, 83, 105, 110, 140]	25–50 mg <i>i.v.</i> in 30–60' min then 50–60 mg <i>q.d.</i> orally
Metoclopramide* [103, 151, 163, 164]	10 mg <i>i.v.</i> then 10–40 mg orally
Haloperidol* [128, 170]	2 mg <i>i.m.</i> 5–10 mg <i>q.d.</i> orally
Amitriptyline [107, 119, 163]	25–90 mg <i>q.d.</i> orally
Carbamazepine [39, 41, 116]	600–1200 mg <i>q.d.</i>
Diphenylhydantoin [171]	200 mg <i>i.v.</i> then 100 mg <i>q.i.d.</i>
Valproic acid [110, 159]	5 mg·kg <sup>-1</sup> <i>q.d.</i> then increase by 250 mg·week <sup>-1</sup> until hiccup stops 500 mg×3 orally
Nifedipine [172, 173]	10–80 mg <i>q.d.</i> orally
Mephenesin [174]	1000 mg orally
Orphenadrine [129, 149, 184, 175]	400 mg orally or 60 mg <i>i.m.</i>

†: only successful trials are reported; \*: can be used in anaesthetized patients. \*\*: average of dosage recommended by different authors;

Recently, baclofen (Lioresal®), a GABA derivative which induces presynaptic motor neuron inhibition and is used as a centrally-active antispasticity agent [176], achieved sustained suppression of chronic hiccup in nine patients [58, 69, 103–107, 165–169]. In five cases, maintenance therapy had to be prescribed. No long-term side-effect was reported. In two cases, treatment could be discontinued after a few months and hiccup did not recur. Our experience with chronic hiccup confirms that baclofen is the drug of choice. Out of nine patients started on baclofen, and in whom follow-up data are available, five were totally relieved of their symptom and two had an important decrease in the length and severity of hiccup spells. Optimal dosage is reached progressively, starting with 5 mg, 12 or 8 hourly, and increasing by 15 mg increments every three days to a maximum daily dosage of 75 mg. Treatment should not be discontinued suddenly. Mild side-effects (somnolence, fatigue, nausea, etc.) are frequent but will often disappear if dosage is reduced.

In addition to chlorpromazine and metoclopramide, a third dopaminergic antagonist has been reported to relieve chronic hiccup. Haloperidol (Haldol®) can be used orally (5–10 mg·day<sup>-1</sup>) or in intramuscular injections

subject [172], the drug was tested on a larger number of patients with persistent hiccup due to various factors. Four out of seven patients responded to nifedipine, and hiccup relapsed when the medication was withdrawn [173]. Recommended daily dosage varies between 30–60 mg. Three anticonvulsant drugs can be effective in terminating persistent hiccup. Carbamazepine (Tegretol®) stopped hiccup in one patient with multiple sclerosis [39, 116], and in one patient with tuberculosis [146]. It can be used orally (200 mg every 6 h) or intramuscularly. Diphenylhydantoin (Dilantin®) has been successful in two patients, and in a third one association with phenobarbital proved to be effective [41, 171]. Valproic acid (Depakine®, Depakene®) efficacy was demonstrated in four out of five patients started on this drug for obstinate hiccup [159]. A dosage of 15 mg·kg<sup>-1</sup> *q.d.* was recommended, with increments every two weeks if necessary. In all four cases, maintenance therapy was required, and the side-effects were troublesome (nausea, mild gastrointestinal bleeding, hepatic toxicity) [159, 179]. In our experience, this drug has been consistently unsuccessful. Muscle relaxants such as mephenesin (Decontractyl®) and orphenadrine (Disipal®, Norflex®) have been effective [129, 174, 175]. Successful treatment



has been reported with the following drugs: benzedrine sulphate [109, 180], apomorphine [109], amyl nitrite [109, 181], benzyl benzoate [42], edrophonium [99], ephedrine [99, 182], atropine [43, 99], scopolamine [86], magnesium sulphate [146], pentazocine [105], niketamide [183], ketamine [184], quinidine sulphate [109, 110], clonazepam [125] and amitriptyline [107, 119, 163, 164]. However, few of these reports concern more than two patients, or convincing controlled data in individual cases.

Several drugs may have to be tried before an effective medication is found: for all of the drugs listed above, the number of successful cases reported equals the number of failures. Successful association of two drugs has only been reported twice [41, 179] but there has been some concern about an increased risk of toxicity, should long-term therapy be necessary [179]. When the treatment is effective, withdrawal should be attempted after a period of time, in order to assess the need for a maintenance therapy.

As a rule, hiccup stops rapidly after the drug treatment is initiated. However, hiccup frequency and amplitude may progressively decrease before hiccup stops completely. There is no need to prolong therapy for more than a few days if the treatment is not effective. Acupuncture [76, 77], hypnosis [69-71] and behavioural therapy [11, 66, 67, 72] have been successfully attempted on a few subjects, and some of our patients have experienced temporary relief with homeopathy and mesotherapy [16].

Interventions on the phrenic nerve have been carried out by means ranging from electrical stimulation [7, 81, 87], and anaesthesia of the nerve [7, 81, 83], to bilateral phrenicotomy [51, 85-90]. Pre-therapeutic evaluation includes diaphragm fluoroscopy and electromyography, in addition to pulmonary function tests, to rule out a contraindication [92]. Although not always successful [43], this method has been shown to bring immediate relief, as for the patient reported by RUBIN *et al.* [91], in whom life-threatening chronic hiccup appeared after myocardial infarction; phrenic crush, performed at the bedside, definitely eliminated hiccup. However, because of potential major respiratory function impairment, phrenic crush or section should not be recommended.

In terminally ill patients, chronic hiccup is frequent, and several factors are often associated [147, 167, 185, 186]. Surprisingly, it is generally disregarded, although it is a major cause of discomfort. Rapid relief is the priority. In general, easily treatable causes such as gastric distension, oesophagitis or metabolic disorders are discovered. Chlorpromazine, meto-clopramide or baclofen should be given if mechanical and aetiological remedies fail.

When deciding on a treatment for hiccup, the balance between risks and benefits must be carefully taken into account. A patient died after ingesting wintergreen oil (methyl salicylate) in order to stop a prolonged hiccup attack [187]. In a series of 42 patients, SAMUELS [7] described four cases of serious side-effects to various treatments: severe neck burns caused by ethyl chloride spraying, respiratory failure after procaine injection in both phrenic nerves, coma following amytal poisoning, and extreme bradycardia causing heart failure after

phrenic faradic stimulation. Two other reports have drawn attention to side-effects of drugs prescribed for persistent hiccup: long-term treatment with valproic acid induced gastrointestinal bleeding [159], and association of chlorpromazine and valproic acid was responsible for severe hepatic toxicity [179]. One of our patients suffered from posterior pharyngeal wounds consecutive to repeated mechanical stimulation [16].

## Conclusions

In contrast with acute spells, persistent hiccups represent a frustrating medical condition. Although aetiological factors are numerous, chronic hiccup is relatively rare, and its pathophysiology is still poorly understood. Further experimental, electrophysiological studies, prospective evaluation of diagnostic procedures and controlled drug trials are required to improve the management of patients presenting with chronic hiccup. At the present time, emphasis should be placed on proposing aetiological treatment whenever possible and assessing carefully the risks and benefits of drug therapy.

In conclusion, it is interesting to note that despite the abundant literature published since Hippocrates, hiccup mechanism is still unclear [188]. The purpose of hiccup remains unknown. The occurrence of hiccup in utero has led to the concept that, in adults, hiccup merely represents the persistence of a primitive reflex. For some authors, hiccup prepares respiratory muscles for their breathing function after birth [189, 190]. Others believe that hiccup is a digestive reflex, preventing amniotic fluid aspiration [191], or caused by gastric distension following fluid ingestion [95]. Lastly, it has been suggested that hiccup does not serve any purpose [192]. French nannies, however, have always known that "enfant hoquetant, enfant bien-portant" (hiccupping child, healthy child). Based on our experience in patients and in a group of seven healthy adults, it seems that in some cases, hiccup may protect the respiratory tract from oesophageal reflux.

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